HHS Public Access

Author manuscript

Behav Processes. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Behav Processes. 2019 August ; 165: 23–28. doi:10.1016/j.beproc.2019.05.017.

Circadian entrainment by food and drugs of abuse

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Abstract

Circadian rhythms organize behavior and physiological processes to be appropriate to the predictable cycle of daily events. These rhythms are entrained by stimuli that provide time of day cues (zeitgebers), such as light, which regulates the sleep-wake cycle and associated rhythms. But other events, including meals, social cues, and bouts of locomotor activity, can act as zeitgebers. Recent evidence shows that most organs and tissues contain cells that are capable of some degree of independent circadian cycling, suggesting the circadian system is more broadly and diffusely distributed. Within laboratory studies of behavior, circadian rhythms tend to be treated as a complication to be minimized, but they offer a useful model of predictable shifts in behavioral tendencies. In the present review, we summarize the evidence that formed the basis for a hypothesis that drugs of abuse can entrain circadian rhythms and describe the outcome of a series of experiments designed to test that hypothesis. We propose that such drug-entrained rhythms may contribute to demonstrated daily variations in drug metabolism, tolerance, and sensitivity to drug reward. Of particular importance, these rhythms may be evoked by a single episode of drug taking, strengthen with repeated episodes, and reemerge after long periods of abstinence, thereby contributing to drug abuse, addiction, and relapse.

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Declarations of Interest: None.

Keywords

Feeding; Entrainable oscillators; Circadian Rhythm; Drug Abuse

Introduction: Light- and Food-entrainable Circadian Oscillators

Endogenous 24-hour circadian rhythms are found in nearly every type of organism on Earth, at the behavioral, anatomical, and molecular level (Harker, 1958). One of the best-known circadian rhythms is the human sleep-wake cycle, characterized by a long active waking period during the day and a shorter sleeping period at night (Monti & Monti, 2008). The timing of this rhythm is set by the day/night cycle, particularly light onset, which acts as a *zeitgeber* – a special kind of environmental cue that dictates the timing of a circadian rhythm in a process known as *entrainment* (Aschoff, 1965). Biological circadian rhythms such as the sleep-wake cycle: have an entrained period very close to 24 hours when a zeitgeber is present; have a "free-running" period that can be several hours longer or shorter than 24 hours when the zeitgeber is absent; and are normally entrained only to cues in a circadian range (Aschoff, 1978; Aschoff, 1965; Harker, 1958). At the cellular level, feedback loops regulate circadian rhythms through paired "clock" genes expressed at opposite times during the 24-hour day (Bell-Pedersen et al., 2005). In animals, specialized "pacemaker" tissues synchronize the oscillatory feedback loops within individual cells, to coordinate groups of cells and produce complex physiological and behavioral rhythms (Takahashi, 1995). The central pacemaker component of the light-entrainable oscillator system is the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore & Silver, 1998).

Although the SCN is the best-known regulator of circadian rhythms, there is considerable evidence that other oscillator systems and zeitgebers exist. One prominent example is the food-entrainable oscillator (FEO) (Mistlberger 1994, recently reviewed in Pendergast & Yamazaki, 2018). The FEO is an endogenous pacemaker that entrains bouts of locomotor activity known as food-anticipatory activity (FAA) that occur 1-2 hours prior to a fixed-time daily meal (Bolles and De Lorge, 1962). SCN-lesioned rats are able to show robust FAA (Stephan, 1981), indicating that the FEO is able to operate independently of the light-entrained SCN pacemaker. As with other biological circadian rhythms, FAA can only occur if the meal is given at an interval of approximately 24 h (Bolles and Stokes, 1965; Boulos and Terman, 1980). After the last timed meal, rats will continue to show a 24-hour activity rhythm for several days under fasting conditions. The disappearance of the behavioral expression of the rhythm does not necessarily mean the rhythm has not continued to free-run: After a period of feeding *ad lib*, fasting can cause a previously entrained meal-related activity rhythm to reemerge (Bolles and Moot, 1973; Coleman et al., 1982).

Within the context provided by these early studies of food-anticipatory activity, Bill Timberlake and his students explored the characteristics and limitations of the FEO. Initial work demonstrated that in rats, the FEO could entrain to 2 meals scheduled at different times of day (White and Timberlake, 1994, 1995), and that meals given at an interval longer than the circadian range (31- and 34-h) caused wheel-running activity peaks approximately 25-26 h after the meal, termed circadian ensuing activity (White and Timberlake, 1999; White et

al., 1999). Note that the 31 h schedule has the property of not repeating a local time of day over 23 days; thus, the 24 h post-event activity peaks suggest one-trial resetting of the oscillator. Similar 24 h post-meal circadian ensuing activity has also been recorded in studies using inter-meal intervals of 29 and 33 h (Bolles and Ogilvie, 1966; Bolles and Stokes, 1965). Evidence supports the physiological and behavioral importance of the meal-entrained rhythms. Along with locomotor activity, fixed daily meals were found to entrain foraging behavior (Boulos and Terman, 1980; Rusak et al., 1988), body temperature and corticosterone rhythms (Krieger 1974a,b, Krieger et al., 1977), liver enzyme production (Stokkan et al.,2001), and duodenal activity (Comperatore and Stephan, 1987). Indeed, circadian oscillators throughout the brain and periphery preferentially entrain to meal times (Damiola et al., 2000; Verwey, Amir 2009; Reviewed in Mistlberger, 2011).

There remain clear and important distinctions between the light- and meal-entrainable circadian systems. In mammals, the primary light-entrainable system is located within the SCN, which can maintain a circadian-length rhythm indefinitely in the absence of light transition cues, while the FEO seems to consist of multiple independently entrainable elements, and food-entrained rhythms appear to damp or decouple fairly rapidly in the absence of the zeitgeber. Moreover, while the FEO appears capable of one-trial resetting; the light-entrained oscillator adapts slowly to large shifts in light/dark phase. These differences are not surprising when viewed from a functional perspective: The day/night cycle changes slowly with the seasons, while optimal timing of feeding opportunities is likely to vary rapidly and unpredictably in an animal's environment (Stephan, 2002). The available evidence suggests that the FEO is a flexible and adaptive system that prepares the organism to find, consume and digest meals (Rosenwasser and Adler, 1986). Under natural conditions, the light and meal-entrained systems would not compete for control of various rhythms; the SCN would act as the master pacemaker synchronizing the rest/activity cycle to day and night, and thus provide the context in which meal timing is optimized (Mistlberger, 2011).

Motivation-entrainable Oscillators

In the mid-1990's, when discussions across the Timberlake and Rebec labs began, it was known that there were a number of light-independent zeitgebers in addition to meals. Free-fed rats can anticipate a palatable snack (Mistlberger and Rusak, 1987), and water-deprived rats can anticipate circadian schedules of water access (Mistlberger, 1992), though these effects tended to be weaker and more difficult to reliably demonstrate. Social interactions (Mrosovsky, 1988), the benzodiazepine triazolam (Turek and Losee-Olsen, 1986) and the glucocorticoid dexamethazone (Horseman and Ehret, 1982) were known to phase shift light-entrainable rhythms. Social stressors or shock presented at a fixed time each day can entrain anticipatory activity and autonomic changes (Ottenweller et al. 1989; Tornatzky et al., 1998; reviewed in Mistlberger and Skene, 2004). Later work would confirm and extend these findings: food-deprived rats can anticipate daily access to a sucrose solution (Pecoraro et al., 2002); free-feeding rats anticipate chocolate (Angeles-Castellanos et al., 2008); and mice anticipate a high fat snack (Hsu et al., 2010). The presence of females restores rhythmic patterns of singing in arrhythmic male zebra finches (Jha and Kumar, 2017), and scheduled daily mating entrains anticipatory activity in male rats (Landry et al., 2012). Although the anticipatory activity observed in these examples is relatively weak compared to FAA, note

that expression does not necessarily mean a weak rhythm (see, for example, Mistlberger et al., 2012).

That motivational stimuli, in general, share an ability to entrain circadian rhythms implies common mediation. A likely site is the central nervous system motivation system, which is also implicated in the addictive properties of drugs of abuse (Robinson and Berridge, 2001). Early evidence that drugs of abuse were also able to entrain circadian rhythms included that methamphetamine (MA), administered chronically via the drinking water or an osmotic pump, restored free-running locomotor, body temperature, and corticosterone rhythms in arrhythmic SCN-lesioned rats (Honma et al., 1987, 1989). Additionally, the dopamine antagonist haloperidol was found to phase-shift the MA-entrained rhythm in SCN-lesioned rats, consistent with a role for dopamine in MA-induced entrainment (Honma and Honma, 1995). Explanatory hypotheses focused on the common ability of the entraining stimuli to evoke arousal or locomotion, most likely working through a component of the FEO (see, for example, Mrozovsky, 1988; Mistlberger, 1994; Hiroshige et al., 1991; reviewed in Mistlberger, 2004). But to our knowledge, no one had articulated the idea that drugs of abuse, with their arousing, locomotor stimulating, and dopamine releasing properties, might share entraining ability, and that entrainment might play a role in addiction. This idea arose quite naturally in discussions among investigators with an interest in drug abuse (Dr. Kosobud, Dr. Rebec) and members of the Timberlake lab (principally Dr. Pecoraro and Dr. Timberlake, and later, Dr. Gillman). These discussions crystalized into a hypothesis that the circadian effects of methamphetamine might be working through the FEO or a related SCN-independent oscillator. A formal test of this hypothesis was initiated in a series of studies to: (1) determine if a “reward-entrainable oscillator” existed; (2) test whether zeitgeber properties are common to drugs of abuse with differing primary mechanisms of action; and (3) elucidate the possible neuropharmacological mechanisms that mediate drug-entrained rhythms. Of particular clinical relevance were the possibilities that a circadian rhythm of drug motivation could be initiated by a single episode of drug-taking, could support and maintain habitual drug use, and might reemerge after weeks or months of abstinence.

The experiments designed to test this hypothesis all used female Wistar rats, were run in constant dim light to eliminate time of day cues, and used rate-limited feeding (consumption limited to no more than two 97 mg pellets/5 min) to prevent meal entrainment that might have arisen secondary to drug effects on feeding and wheel running. We first demonstrated that MA injections given at 24 h intervals entrained anticipatory wheel running, and that a transient elevation in wheel running recurred 24 h after the final injection (Kosobud et al., 1998). MA injections given at 31 h intervals were followed 24 h later by wheel running, similar to circadian ensuing activity observed after 31 h meal delivery in intact (Pecoraro et al., 2000) and SCN-lesioned rats (Kosobud et al., 2007). A series of studies demonstrated 24 h anticipation and 31 h ensuing activity for fentanyl and nicotine, but not haloperidol or saline, (Gillman et al., 2008, 2009). Thus, initial experiments generally supported the hypothesis that abused drugs had entraining properties similar to meals, though the observed wheel-running bouts were generally not as robust.

The next series of studies focused on nicotine. As with food-anticipatory activity, nicotine-entrained activity can occur under a variety of lighting conditions, including fixed light/dark,

constant light, and a variable light/dark schedule (Gillman et al 2013). Rats administered 2 to 4 daily nicotine injections entrained only to the first injection of the day (Gillman et al., 2010), an observation interesting in light of the importance of the first cigarette of the day to nicotine dependence and relapse (Toll et al, 2007; Fagerstrom, 2003). This demonstrates a difference between food and drug entrainment, as earlier work had found that rats could entrain to two large daily meals (White and Timberlake, 1994).

In addition, these studies suggested that two distinct types of circadian locomotor activity were entrained, one which anticipated the drug injections (termed “pre-drug activity”) and an independent rhythm associated with the direct effects of the drug (termed “post-drug activity”) (Gillman, 2008). These rhythms appeared to be both locomotor activity- and reward-related. Given that locomotor activity itself is known to have weak entraining effects (reviewed in Mistlberger, 2004), it is possible that the post-injection activity might be in part or all due to locomotor entrainment. Circadian pre- and post-drug activity were present in some form in ethanol, nicotine, methamphetamine, and fentanyl with some evidence of dose-dependency (Gillman, et al., 2013). Some pre- and post- activity could also be observed for p-hydroxyamphetamine, an analog of amphetamine which does not readily cross the blood/brain barrier, and in some cases, saline injections were observed to entrain wheel-running activity as well, possibly mediated through the transient increase in wheel-running provoked by handling and injection (Gillman et al., 2013).

Finally, seven drugs that have been proposed or used for treatment of drug abuse were tested for their ability to alter activity entrained by nicotine injections (Gillman et al., 2013). All drugs were tested at a single dose shown to alter a behavioral or physiological effect of nicotine (if tested) or of another abused drug. This work demonstrated that the pre- and post-injection activity showed different patterns of susceptibility and resistance to drug manipulations, consistent with mediation by different neurochemical mechanisms. Pre-nicotine anticipatory activity was reduced by administration of the μ-opioid receptor antagonist naltrexone, the orexin-1 antagonist SB-334867, and the glutamate AMPA/kainate antagonist topiramate. Post-nicotine activity was reduced by these same three drugs but also by several drugs that had no effect on pre-injection activity, including drugs targeting nicotinic acetylcholine (varenicline, mecamylamine), glutamatergic NMDA receptors (acamprosate), and dopamine receptors (buproprion).

This work provided affirmative answers to our first two questions: there is evidence of a drug-entrainable oscillator, sensitive to the general class of abused drugs. In particular, the results showing that treatment medications suppress pre- and post-injection nicotine-entrained activity are consistent with a role for circadian rhythms in the maintenance of addiction. We were unable to resolve the question of the relationship of the drug-entrained oscillator to the feeding-entrained oscillator, or address the neural basis of drug entrainment. Nevertheless, some hints at answers may be found in what is now known about the neural basis of motivated behavior, and of light and feeding-entrained circadian rhythms.

Neural Mechanisms of Entrainment to Rewarding Stimuli:

At the same time that Dr. Timberlake was advocating that scientists look outward, to understand behavior as existing within a broad system that included an organism’s

capabilities, what it needed, and what it knew, the study of behavior was largely moving in the opposite direction, towards increasingly cellular and molecular approaches. Initially, this was reflected in attempts to find a “master” coordinator that regulated feeding entrainment, similar to the role of the suprachiasmatic nucleus for light/dark entrainment. The continued failure of these efforts suggests that the meal-entrained circadian system is most likely diffusely distributed (Davidson, 2009). A number of brain regions that can support, but are not required, for meal-related entrainment have been identified, with roles in feeding, energy balance, learning, and motivation (reviewed in Verwey and Amir, 2009). The motivation system remains the most likely site for an overlap between the drug- and meal-entrained systems.

In mammals, exposure to natural rewards such as food activates the mesocorticolimbic system of the brain, defined by the dopamine neurons in the midbrain ventral tegmental area and their targets, principally the nucleus accumbens. Early work identified an association between feeding and the release of the dopamine in the nucleus accumbens (Hernandez & Hoebel, 1988). Dopamine release in this region has also been linked to the consumption of large amounts of sucrose (Rada et al., 2005), the formation of monogamous pair bonds in prairie voles (Aragona et al., 2006), and romantic love in humans (Fisher et al., 2005). Several classes of addictive drugs acutely stimulate the release of dopamine in the nucleus accumbens, including nicotine, ethanol, amphetamine, cocaine, and several types of opiates (Di Chiara and Imperato, 1988). This early work suggested an association of dopamine release with ‘liking’, or hedonic value of rewards. But later work indicated that it is more properly associated with a variety of motivation-related functions, including learning reward probabilities and predicting when rewards will occur (Shultz et al., 1997), activation and/or arousal (Robbins and Everitt, 2006), willingness to expend effort to achieve a goal (Salamone et al., 2016), learning about the motivational significance of stimuli (Wise, 2004), and the power stimuli thereby gain to initiate and guide behavior (Berridge and Robinson, 2016). Moreover, the actions of dopamine are now understood in a broader context that includes interactions with glutamate (Sesack et al., 2003), a key driver of the drug craving that develops following repeated drug exposure.

Both dopamine and glutamate are sensitive to circadian regulation. Dopamine, which acts to modulate the responsiveness of neurons in the mesocorticolimbic circuit (Kiyatkin and Rebec, 1999; Moore et al., 2011), shows daily fluctuations in extracellular levels (Castañeda et al., 2004; Hood et al., 2010). Importantly, changes in dopamine tone are governed in large part by the dopamine transporter (DAT), a trans-membrane protein that clears dopamine from the extracellular space after its release from neurons. DAT is responsible for the diurnal variations in dopamine tone (Ferris et al., 2014). Drugs of abuse can override this system by eliciting transient increases in dopamine transmission (Covey et al., 2014). Cocaine, for example, acts directly on DAT, and photoperiodic modulation of DAT in the prefrontal cortex, a key driver of drug craving, strongly influences susceptibility to relapse in rats tested for cocaine-induced reinstatement of conditioned place preference (Sorg et al., 2011). Circadian modulation of DAT appears to be a key factor in addictive behavior. Moreover, diurnal variations in dopamine tone are directly related to expression of the clock protein PERIOD2 (PER2) in dorsal striatum, a region of the basal ganglia critical for habit learning (Yin et al., 2004). Manipulations that deplete dopamine levels blunt the PER2 rhythm, which

can be restored by activation of D2 dopamine receptors (Hood et al., 2010). In fact, this study also revealed that timed activation of these receptors can entrain the PER2 rhythm. Similarly, a single injection of a D2 receptor agonist can shift the timing of circadian food anticipation (Smit et al., 2013), whereas this rhythm is attenuated by D1 and D2 receptor antagonists (Liu et al., 2013). Subsequent work has shown a critical role for D1 receptors in synchronizing circadian oscillators in motivated behavior (Gallardo et al., 2014). Thus, activation of the striatal dopamine system can shift circadian oscillators and perhaps drive anticipation of drug and natural rewards.

Glutamate, the dominant excitatory amino acid in the brain, is essential for cognition, learning, and memory. Like dopamine, glutamate is cleared after its release by transporter proteins. A family of five sodium-dependent, high-affinity transporters, collectively known as excitatory amino acid transporters, remove glutamate from the synapse. Two of these, glutamate transporter 1 (GLT1) and glutamate-aspartate transporter (GLAST), are responsible for up to 90% of brain glutamate uptake (Danbolt, 2001). Although glutamate transporters are governed by multiple mechanisms, growing evidence indicates that glutamate transporters are regulated in a circadian fashion (Chi-Castañeda and Ortega, 2018). Both GLAST and GLT1 are controlled by the circadian clock gene, Per2, which can influence the diurnal variation in the intake of alcohol and perhaps other abused substances (Spanagel et al., 2005). Interestingly, the reinstatement of cocaine seeking in rats previously trained to self-administer the drug appears to be driven by a decrease in GLT1 expression in the core region of the nucleus accumbens (Sari et al., 2009; Knackstedt et al., 2010), which receives direct glutamate input from the medial prefrontal cortex, a pathway known to drive drug craving (McFarland and Kalivas, 2001). Up-regulation of GLT1 prevents reinstatement, and selective blockade of GLT1 in the accumbal core reverses this effect (Fischer et al., 2013). Thus, GLT1 is critically involved in shaping the glutamate signal in a forebrain region critically involved in drug relapse (Kalivas et al., 2009).

The glutamate signal is further modulated by the cystine/glutamate exchanger (xCT), which takes up cystine for the production of glutathione, an antioxidant, and releases glutamate into extracellular fluid where it can act on pre-synaptic metabotropic glutamate receptors to inhibit further glutamate release (Moran et al., 2005). In effect, both GLT1 and xCT operate together to, respectively, dampen glutamate transmission by clearing it from the synapse and inhibiting further release. Both are found primarily in the plasma membrane of astrocytes. Remarkably, astrocytes in the SCN drive the molecular oscillations that regulate circadian rhythms. Rescue of the astrocyte circadian clock in otherwise arrhythmic mice is sufficient to rescue rhythmic behavioral activity (Brancaccio et al., 2019). Moreover, these authors found that astrocytic control of circadian behavior depends on the control of glutamate signaling, although the precise role of GLT1, GLAST, or xCT remains to be established.

Finally, glutamate output from cortex also targets the dorsal striatum and growing evidence suggests that circadian rhythmicity plays a role in the emergence and expression of Huntington’s disease (HD), a dominantly inherited condition characterized in part by dysregulation of glutamate transmission, including expression of GLT1 (Estrada-Sanchez and Rebec, 2012). Both HD patients and transgenic animals that model HD show disruptions in circadian rhythmicity (Morton, 2013). Interestingly, time-restricted feeding of HD mice

improves both motor symptoms and circadian rhythms (Wang et al., 2018). Direct alterations of the circadian clock modulate the toxicity of the HD gene, establishing a functional role for the clock in a neurodegenerative disease (Xu et al., 2019). In fact, circadian disruptions are emerging as common elements across multiple neurodegenerative conditions (Musiek and Holtzman, 2016), highlighting the potential therapeutic benefit of further research in this area.

It appears, therefore, that mechanisms in the SCN that control glutamate and regulate daily fluctuations in behavior also operate in the cortical-accumbal system that drives addiction. It may be the case that light, food, and motivation-related entrainment, despite considerable variation in anatomical organization and expression, converge on a number of fundamental mechanisms to achieve stable timing. The challenge ahead will be to reconcile what is known at the level of neurochemistry with behavior.

Circadian rhythms in health and disease

In summary, a series of investigations in the Timberlake lab and at other institutions set the outlines of a circadian system in rats that is entrainable by drugs of abuse and is at least partially independent of the light-entrained, SCN-centered circadian system. This drug-entrained system displays many similarities to the food-entrainable oscillator, in that it engages anticipatory locomotor activity preceding the zeitgeber in the absence of time-of-day cues, and also transient increases in activity that appear roughly 24 hours after a single encounter with the zeitgeber. As with other circadian rhythms, drug-entrained circadian activity can persist at 24 hour intervals for several days. This activity may reflect circadian tuning of motivation to prepare for repeated drug intake at times of day in which drugs have been encountered in the past. Thus, it is potentially both a target for intervention and a useful model for studying neural and physiological changes associated with the onset of craving. Given what is now known about the wide distribution of entrainable cells throughout the brain and periphery, and the role of dopamine and glutamate in circadian rhythms, it may be time to revisit the role that entrainment may play in drug craving, habitual drug use, and relapse.

Acknowledgements:

Our thanks to Joseph K. Leffel, II, for invaluable assistance in completing this work.

Funding: Research summarized in this review was supported by NIDA grants DA017692, DA11092 and DA02451; NIMH grant 37892, and by the Indiana Alcohol Research Center (NIAAA grant P60AA07611).

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Highlights

- Circadian rhythms are physiological and behavioral rhythms that have a daily cycle.
- The most well-known circadian rhythm is the rest/activity cycle, entrained by transitions to daylight and darkness.
- But events with motivational significance, particularly food, but also social or sexual opportunities, and stressful events, can also entrain rhythms.
- Drugs of abuse also entrain circadian rhythms.
- These drug-entrained rhythms may play a role in drug seeking, taking, addiction and relapse.